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CLINICAL AND LABORATORY OBSERVATIONS

Viral infections in interferon-γ receptor deficiency

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Interferon-γ receptor deficiency is a recently described immunodeficiency that is associated with onset of severe mycobacterial infections in childhood. We describe the occurrence of symptomatic and often severe viral infections in 4 patients with interferon-γ receptor deficiency and mycobacterial disease. The viral pathogens included herpes viruses, parainfluenza virus type 3, and respiratory syncytial virus. We conclude that patients with interferon-γ receptor deficiency and mycobacterial disease have increased susceptibility to some viral pathogens. (J Pediatr 1999;135:640-3)

Humans with absent or diminished response to interferon-γ caused by nonfunctional or dysfunctional IFN-γ receptors have recently been described.[1-8] These patients acquire mycobacterial infections that are frequently due to low virulence species such as *Mycobacterium avium* complex and are often disseminated and refractory to treatment. Infections with *Salmonella* species and other intracellular bacteria also occur in patients with IFN-γ receptor deficiency.[1,5,7] However, increased susceptibility to viral infections has not been recognized previously. We have identified 4 patients with IFN-γ receptor dysfunction and symptomatic viral infections with either DNA or RNA viruses. This recently recognized aspect of human IFN-γ receptor deficiency broadens the phenotype for consideration of this newly described primary immunodeficiency disease.

See editorial, p. 543.

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CASE REPORTS

Patient 1 was born in the United States to consanguineous Pakistani parents. He was well until 8 months of age when he developed fever, hepatosplenomegaly, pneumonia, and anemia. A diagnosis of disseminated MAC infection was made. Subsequently, he was found to have complete absence of IFN-γ responsiveness caused by a homozygous mutation in the IFN-γ receptor 1 gene[6] (Table). At age 3 years, he developed disseminated cytomegalovirus infection with pneumonia, diagnosed by positive cultures of blood and bronchoalveolar lavage fluid, as well as visualization of typical cytomegalic inclusion cells in the latter; he required mechanical ventilation and prolonged therapy with ganciclovir, administered intravenously. Two months later, he developed parainfluenza virus type 3 pneumonia, diagnosed by culture of bronchoalveolar lavage fluid, which was complicated by respiratory failure requiring mechanical ventilation. Five months later he

CMV	Cytomegalovirus
HSV	Herpes simplex virus
IFN-γ	Interferon-γ
MAC	*Mycobacterium avium* complex
RSV	Respiratory syncytial virus
VZV	Varicella zoster virus

had severe respiratory syncytial virus pneumonia, diagnosed by culture of bronchoalveolar lavage fluid, for which mechanical ventilation was again required. This infection was treated with aerosolized ribavirin and intravenous RSV immune globulin (RespiGam; Medimmune, Gaithersburg, Md). On 2 subsequent occasions he developed pneumonia with respiratory failure requiring mechanical ventilation, although no specific causative agents were identified.

Patient 2 was born in the United States to parents of English and Portuguese descent who were not known to be consanguineous. He was well as an infant, but at age 2 years he developed fever, lymphadenopathy, and hepatosplenomegaly caused by disseminated *M fortuitum* and MAC infections.[3] He had no detectable IFN-γ responsiveness because of a homozygous mutation in IFN-γ receptor 2. At age 3 he developed oral ulcers, vesicular skin lesions, and severe retrosternal pain associated with eating, which resulted in weight loss. Herpes simplex virus was isolated from an oral lesion. Within 3 days of beginning oral acyclovir therapy (60 mg/kg/d), his appetite improved, and he was back to normal within 1 week. Acyclovir therapy was continued for 3 weeks. Approximately 5 weeks later, he had a recurrence of oral lesions similar in appearance to those of the prior episode, not associated with retrosternal pain. He was treated with acyclovir, administered orally, without further recurrence of lesions.

Patient 3 had complete absence of IFN-γ receptor function because of compound heterozygous mutations in the IFN-γ receptor 1.[7] She was vaccinated with bacille Calmette-Guérin as an infant and first came to medical attention at age 4 months with fever, pneumonia, axillary lymphadenopathy, hepatomegaly, and a vesicular skin rash. At first, appearance of the rash was typical of varicella infection, but new vesicles formed for at least 10 days, and the rash took on the appearance of Kaposi's varicelliform eruption. Serologic testing revealed presence of varicella-specific IgM antibody; culture was not performed. The rash resolved with acyclovir treatment. Cultures from a lymph node biopsy specimen obtained at that time grew bacille Calmette-Guérin; biopsies of lung and liver were not performed. Subsequent infections included disseminated MAC, disseminated *M kansasii*, and *Listeria monocytogenes* meningitis.

Patient 4 was born to nonconsanguineous parents of Korean and African descent. He was well until age 6 years when he developed multifocal osteomyelitis caused by *M kansasii*, and since then he has had recurrent disseminated infections with numerous nontuberculous mycobacteria. Genetic analysis showed heterozygosity for a mutant *IFN-γ receptor* allele containing a single nucleotide insertion (817insA), which codes for a protein with dominant negative function.[8] At age 17 years he developed shortness of breath, with numerous vesicular skin, pharyngeal, and lingual lesions. Patchy infiltrates were seen on chest x-ray film, and mechanical ventilation was required for progressive respiratory failure. Electron microscopy performed on scrapings from skin lesions showed viral particles consistent with a herpes group virus, and serology confirmed a diagnosis of acute varicella. He was treated with intravenous acyclovir and gradually improved.

DISCUSSION

IFN-γ is a pleiotropic cytokine produced by activated T lymphocytes and natural killer cells. It acts via its cognate receptor to directly stimulate antimicrobial activities of monocytes/macrophages, and it plays a major role in activation of cell-mediated immunity. IFN-γ was first recognized for its in vitro antiviral activity.[9] Its importance in the in vivo immune response has since been confirmed in mice with targeted disruptions of the *IFN-γ* or *IFN-γ receptor* genes. These knockout mice have increased susceptibility to a wide spectrum of infectious agents, including mycobacteria,[10-13] bacteria,[14-16] parasites,[17-20] and viruses. After experimental inoculation, infections with the DNA viruses HSV,[21,22] murine CMV,[23] murine gammaherpesvirus,[24] and vaccinia virus[25] are more prolonged and/or severe in these knockout mice than in normal mice. Single-strand RNA viruses pathogenic in these mouse models include Theiler's virus,[26] lymphocytic choriomeningitis virus,[25,27] and mouse hepatitis virus (a coronavirus).[28]

Patients with nonfunctional or dysfunctional IFN-γ receptors clearly have increased susceptibility to mycobacterial infections. These infections tend to be severe and difficult to treat and have been the major recognized cause of morbidity and mortality in this patient group. *Salmonella* and *Listeria monocytogenes* infections have also been described in a subset of patients with IFN-γ receptor deficiency and mycobacterial infections.[1,5,7] However, increased susceptibility to viral infections in patients with IFN-γ receptor deficiency has not been previously recognized. In each of the patients in this report, viral infection was symptomatic, and infection was severe in several instances. All patients had herpes virus infections, paralleling the heightened susceptibility of IFN-γ and IFN-γ receptor knockout mice to herpes viruses.[21-24] Patient 1 also had severe infections with parainfluenza virus type 3 and RSV, both of which are single-stranded RNA viruses.

Our clinical experience differs from that reported previously by others. Sixteen French children with idiopathic disseminated bacille Calmette-Guérin infection, identified in a national retrospective survey, were reported to have had normal clinical courses and frequency of infections with common

Table. Patients with IFN-γ receptor deficiency: Details of infections

Patient No.	IFNγR defect	Viral infection	Age	Manifestations	Diagnostic tests	Therapy	Comments
1	IFNγR1; 201-2A→G	CMV	3 y	Viremia, pneumonia	Culture	IV ganciclovir, MV	Intubated 19 d
		PIV-3	3 y	Pneumonia	Culture	MV	Intubated 7 d
		RSV	3.5 y	Pneumonia	Culture	Ribavirin, RSV immune globulin, MV	Intubated 11 d
2	IFNγR2; 278delA,G	HSV	3 y	Gingivostomatitis, esophagitis, skin lesions	Culture	Oral acyclovir	
3	IFNγR1; 561del4; 373+1G→T	VZV	4 mo	Skin lesions	Serology	IV acyclovir	New vesicle formation for at least 10 d
4	IFNγR1; 817insA	VZV	17 y	Pneumonia, skin lesions	EM, serology	IV acyclovir, MV	Intubated 4 d; all skin lesions crusted by day 12

MV, Mechanical ventilation; *IV,* intravenous; *PIV,* parainfluenza virus; *VZV,* varicella zoster virus; *EM,* electron microscopy.

childhood pathogens, including varicella.[29] However, genetic and immunologic defects in those patients were not known and are likely to be heterogeneous, making comparison with the patients in this report difficult. In a small group of patients with IFN-γ receptor deficiency, Jouanguy et al[30] reported normal recovery from infections caused by rotavirus, rhinovirus, influenza virus, RSV, and varicella zoster virus and positive serologies for HSV, Epstein-Barr virus, and CMV without histories of clinical disease. Explanations for this apparent discrepancy include the possibilities that: (1) some patients with IFN-γ receptor dysfunction may have additional genetic factors that affect their susceptibility to viral infections; (2) viral disease may be favored by concomitant mycobacterial infection and poor clinical status; and (3) as more children with IFN-γ receptor mutations are identified, a broader spectrum of infection susceptibility may become apparent.

Although disseminated infection with non tuberculous mycobacteria is the most common clinical presentation of IFN-γ receptor deficiency in the patients described to date, our experience suggests that the frequency and severity of viral infections may also be increased in patients with this primary immunodeficiency. IFN-γ receptor deficiency should be included in the differential diagnosis in children with severe viral infections. In patients known to have IFN-γ receptor deficiency, viral pathogens should be considered in appropriate clinical settings.

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